

RECEIVED

JAN - 8 2014

TONY R. MOORE, CLERK  
WESTERN DISTRICT OF LOUISIANA  
LAFAYETTE, LOUISIANA

UNITED STATES DISTRICT COURT  
WESTERN DISTRICT OF LOUISIANA  
LAFAYETTE DIVISION

IN RE: ACTOS® (PIOGLITAZONE)  
PRODUCTS LIABILITY LITIGATION

MDL No. 6:11-md-2299

JUDGE DOHERTY

This Document Applies To:  
*Allen, et. al. v. Takeda Pharmaceuticals  
North America, Inc., et al.*  
(Case No. 12-cv-00064)

MAGISTRATE JUDGE HANNA

**MEMORANDUM RULING:**  
**HERBERT BARTON GROSSMAN, M.D.**

This multidistrict litigation arises from product liability claims against the manufacturer and marketer of Actos® and other drugs containing pioglitazone. Pending before this Court is the Defendants' Motion to Exclude Testimony of Plaintiffs' Expert, Herbert Barton Grossman, M.D.<sup>1</sup> For the following reasons, the Defendants' Motion will be DENIED IN PART AND GRANTED IN PART.

**EVIDENCE AT ISSUE**

Herbert Barton Grossman is a medical doctor and urologic oncologist, who works as a Clinical Professor of Oncology at the University of Texas M.D. Anderson Cancer Center in Houston, Texas. He has submitted a 57-page report,<sup>2</sup> together with an attachment listing the case materials he has reviewed.

---

<sup>1</sup> Rec. Doc. 3465. This motion has been urged on behalf of all named defendants in this matter. The Memorandum in Support of Defendants' Motion to Exclude Testimony of Plaintiffs' Expert Herbert Barton Grossman, M.D. is found at Rec. Doc. 3465-1 ["Memorandum"]; the Plaintiffs' Memorandum of Law in Opposition to Defendants' Motion to Exclude Testimony of Plaintiffs' Expert Herbert Barton Grossman, M.D. is found at Rec. Doc. 3637 ["Opposition"]; and the Defendants' Reply in Support of Defendants' Motion to Exclude Testimony of Plaintiffs' Expert Herbert Barton Grossman, M.D. is found at Rec. Doc. 3669 ["Reply"]. For these purposes only, the Court will make no distinction between and among defendants as, for these purposes, there is no legal distinction to be made.

<sup>2</sup> "The Grossman Report" was submitted by the Plaintiffs as Exhibit 2 to the Opposition, and was submitted by the Defendants as Omnibus Exhibit C4. "The Grossman Deposition" was submitted by the Defendants as Omnibus Exhibit B4.

Dr. Grossman has developed the following opinions:

- It is my opinion that Actos® (pioglitazone), a Peroxisome Proliferator-Activated Receptor Agonist (PPAR), has both alpha and gamma activity.
- It is my opinion that dual agonists, as well as gamma agonist agents are capable of causing bladder tumors in laboratory animals.
- It is my opinion that Actos® can cause bladder cancer in exposed individuals.
- It is my opinion that there is a dose-response relationship between the increased risk of developing bladder cancer and exposure to Actos® (pioglitazone).
- It is my opinion that bladder cancer in an Actos® (pioglitazone)-exposed person typically presents as transitional cell carcinoma, also known as urothelial carcinoma.
- It is my opinion that Actos® (pioglitazone) acts as a promoter of bladder tumors in humans and may induce tumors of the bladder.
- It is my opinion that the bladder cancers found in patients exposed to Actos® (pioglitazone) are similar to the bladder cancers found in the unexposed population.
- It is my opinion that bladder cancer is a significant cause of morbidity and mortality in individuals who develop the disease.
- It is my opinion that the recurrence rate of bladder cancer is among the highest of all cancers.
- It is my opinion that bladder cancer is among the most expensive cancers to treat and imposes a significant burden on the patient and the healthcare system.

The Defendants' Motion does not challenge Dr. Grossman's qualifications,<sup>3</sup> nor the relevance of his opinions. The Defendants' sole challenge is to the reliability of Dr. Grossman's opinions.

---

<sup>3</sup> In an argument similar to the one used with the Daubert briefing on Dr. Delacroix, the Defendants' Reply dedicates almost half a page – "because Plaintiffs choose to raise Dr. Grossman's qualifications in support of their insistence that he properly analyzed all studies as an expert in etiology and epidemiology" (Reply, at 2) – proving that Dr. Grossman has admitted that he is not an epidemiologist and that he has not previously played a role (whether in clinical trials, in his clinical practice, or as an expert) in identifying the causes of bladder cancer. As before, the Defendants did not include any actual argument suggesting that Dr. Grossman is, therefore, unqualified as an urologic oncologist, nor did they tie this particular argument to any relevant *legal* issue, *i.e.*, the application of Rule 702. Considering the lack of actual argument, together with the lack of any argument about Dr. Grossman's qualifications in the Defendants' Memorandum, this Court finds that the Defendants' somewhat questionable discussion in the Reply Brief as to Dr. Grossman's qualifications is not intended as a challenge to Dr. Grossman's qualifications as an expert urologic oncologist. Furthermore, to the extent the rather dubious discussion is intended

## LAW AND ANALYSIS

### I. APPLICABLE LAW

While state law governs the Plaintiffs' claims in this matter, the Federal Rules of Evidence control the admission of expert testimony.<sup>4</sup> Under the Federal Rules of Evidence, "relevant" evidence is admissible, while irrelevant evidence not admissible.<sup>5</sup> Evidence is "relevant" if it has any tendency to make a fact more or less probable than it would be without the evidence, and the fact being proven or disproven is of consequence in determining the action.<sup>6</sup> The party seeking to have expert opinion testimony admitted into evidence bears the burden of demonstrating, by a preponderance of the evidence, that the expert's findings and conclusions are based on the scientific method and, therefore, are reliable.<sup>7</sup>

The Federal Rules of Evidence require that a judge, faced with a proffer of expert scientific testimony, must begin by determining, pursuant to Rule 104(a), whether the expert is proposing to (i) testify to scientific knowledge (ii) that will assist the trier of fact to understand or determine fact in issue.<sup>8</sup> This will require a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or

---

as a formal challenge to Dr. Grossman's qualifications, this Court finds the argument wholly without merit and boarding on specious. As a general matter, the Plaintiffs are not limited to using only epidemiologists in proving general causation; equally importantly, each expert who has been accepted and allowed to testify as to his or her opinions has had the experience of doing so for the first time. Dr. Grossman's lack of experience *as an expert*, in and of itself, does not nullify *his professional accomplishments, education, training and experience*.

<sup>4</sup> Huss v. Gayden, 571 F.3d 442, 452 (5<sup>th</sup> Cir. 2009), *citing* Mathis v. Exxon Corp., 302 F.3d 448, 459 (5<sup>th</sup> Cir. 2002).

<sup>5</sup> F.R.E. 402.

<sup>6</sup> F.R.E. 401.

<sup>7</sup> Moore v. Ashland Chemical, Inc., 151 F.3d 269, 276 (5<sup>th</sup> Cir. 1998) (*en banc*).

<sup>8</sup> Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 592, 113 S.Ct. 2786, 2796, 125 L.Ed.2d 469 (1993).

methodology properly can be applied to the facts in issue.<sup>9</sup> This requirement is found in Rule 702 of the Federal Rules of Evidence, which reads as follows in its entirety:

A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:

- (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
- (b) the testimony is based on sufficient facts or data;
- (c) the testimony is the product of reliable principles and methods; and
- (d) the expert has reliably applied the principles and methods to the facts of the case.

In the United States Supreme Court's landmark decision in Daubert v. Merrell Dow Pharmaceuticals, Inc., the Court acknowledged the existence of a federal court's gatekeeping role with regard to expert scientific opinion testimony, characterizing that role as one ensuring that such evidence meet the requirements of both reliability and relevance.<sup>10</sup> "Reliability" as discussed in Daubert refers to *evidentiary* reliability, *i.e.*, trustworthiness, rather than *scientific* reliability, which asks whether application of the principle produces consistent results, a distinction often blurred by Defendants' arguments. In a case involving scientific evidence, evidentiary reliability is based upon scientific validity, which asks whether the principle supports what it purports to show.<sup>11</sup>

The objective of this requirement is to make sure that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same

---

<sup>9</sup> Id., 509 U.S. at 592-93; Moore, 151 F.3d at 276.

<sup>10</sup> Moore, 151 F.3d at 275.

<sup>11</sup> Daubert, 509 U.S. at 590 n.9.

level of intellectual rigor that characterizes the practice of an expert in the relevant field.<sup>12</sup> The Supreme Court identified several non-exclusive factors a court should consider in determining whether proffered scientific opinion testimony is sufficiently reliable to permit admission into the record.<sup>13</sup> Those factors are:

- whether the expert's theory can be or has been tested;
- whether the theory has been subject to peer review and publication;
- the known or potential rate of error of a technique or theory when applied;
- the existence and maintenance of standards and controls; and
- the degree to which the technique or theory has been generally accepted in the scientific community.<sup>14</sup>

Several years later, the Supreme Court clarified when it held the gatekeeping role applied to all types of expert opinion testimony, not just scientific evidence, and revisited the reliability analysis.<sup>15</sup> Moreover, the Supreme Court reiterated that a court must have considerable leeway in deciding, in a particular case, how to go about determining whether particular expert testimony is reliable.<sup>16</sup> Therefore, the test of reliability is flexible and there is no necessary or exclusive list of factors that must exist in order for a particular opinion to be admissible.<sup>17</sup>

Daubert makes clear that the factors it mentions do not constitute a definitive checklist or test. Daubert adds that the gatekeeping inquiry must be tied to the facts of a particular case. We agree with the Solicitor General that the facts identified in Daubert may or may not be pertinent in assessing reliability, depending on the nature of the issue, the expert's

---

<sup>12</sup> Kumho Tire Company, Ltd. v. Carmichael, 526 U.S. 137, 152, 199 S.Ct. 1176, 143 L.Ed.2d 238 (1999). See also Brown v. Illinois Central Railroad Co., 705 F.3d 531, 535 (5<sup>th</sup> Cir. 2013).

<sup>13</sup> See discussion, 509 U.S. at 594-595.

<sup>14</sup> Moore, 151 F.3d at 275.

<sup>15</sup> Kumho Tire, 526 U.S. at 141-142.

<sup>16</sup> Id., 526 U.S. at 152.

<sup>17</sup> Id., at 141-142, 149.

particular expertise, and the subject of his testimony. The conclusion, in our view, is that we can neither rule out, nor rule in, for all cases and for all time the applicability of the factors mentioned in Daubert, nor can we now do so for subsets of cases categorized by category of expert or by kind of evidence. Too much depends upon the particular circumstances of the particular case at issue.<sup>18</sup>

In the Fifth Circuit, “[t]o determine whether proffered testimony is reliable, the trial court must make ‘a preliminary assessment of whether the reasoning or methodology underlying the testimony is . . . valid and of whether that reasoning or methodology properly can be applied to the facts in issue.’”<sup>19</sup> Further, “[t]o establish reliability under Daubert, an expert bears the burden of furnishing ‘some objective, independent validation of [his] methodology.’”<sup>20</sup> In doing so, “[t]he expert’s assurances that he has utilized generally accepted [principles] is insufficient.”<sup>21</sup>

In Brown the Fifth Circuit held that the trial court did not abuse its discretion where an expert testified that offered opinions were reliable merely upon and because of “education and experience” and did not engage in or rely upon a credible methodology, particularly in the face of evidence in opposition to those opinions. Standing alone then, it is insufficient for an expert to base his or her opinion on education and experience alone, especially in the face of evidence to the contrary.

## II. ANALYSIS

Plaintiffs bear the ultimate burden on this issue, thus, this Court will first look to Plaintiffs’ *prima facie* showing. The task for this Court within this Motion, as the gatekeeper, is

---

<sup>18</sup> Kuhmo Tire, at 150 (citations and quotation marks omitted).

<sup>19</sup> Brown v. Illinois Central Railroad Co., 705 F.3d 531, 535 (5th Cir. 2013) (*quoting* Daubert, 509 U.S. at 592–93).

<sup>20</sup> Brown, 705 F.3d at 536 (*quoting* Moore, 151 F.3d at 276).

<sup>21</sup> Id. (*quoting* Moore, 151 F.3d at 276).

to determine whether Dr. Grossman has the necessary qualifications, employed a required process, methodology, rely upon sufficiently sound scientific evidence and comport with the inquiry and factors identified in Daubert, within his area of expertise so as to be allowed to pass the gatekeeper inquiry. The specific analysis of this issue will begin with consideration of the Plaintiffs' evidence in support of their *prima facie* case, and then proceed to consideration of the Defendants' specific challenges.

**A. Dr. Grossman's Report, Opinions, and Supporting Evidence**

The body of the Grossman Report is 50 pages in length, with an attached list of the 81 publications references upon which Dr. Grossman relied in developing his opinions, along with a list of the case materials he reviewed in developing his opinions and producing his report.

The Grossman Report contains:

- a description of his qualifications;<sup>22</sup>
- a list of the opinions that he has developed in this matter;<sup>23</sup>
- a discussion of the applicable general principles and the methodology he used in reaching his opinions;<sup>24</sup>
- a description of the process by which bladder cancer develops and progresses;<sup>25</sup>
- a discussion of other risk factors for bladder cancer;<sup>26</sup>
- a brief description of Actos®;<sup>27</sup>

---

<sup>22</sup> The Grossman Report, at 1-4.

<sup>23</sup> Id. at 4-5.

<sup>24</sup> Id. at 5-13.

<sup>25</sup> Id. at 13-18.

<sup>26</sup> Id. at 18-22.

<sup>27</sup> Id. at 23-24.

- an extensive discussion of the scientific evidence he considered in developing his opinions;<sup>28</sup>
- the methodology he used to distinguish risk factors;<sup>29</sup> and
- his conclusions.<sup>30</sup>

This Court has conducted an exhaustive review of the briefs, the exhibits submitted in support of both parties' arguments, and all studies and reports, including those specifically of Dr. Grossman that are under challenge with the instant motion. This Court finds, as a threshold matter, that Dr. Grossman is qualified to develop the opinions he has reached in this case, that as a threshold matter, he relied on standard and accepted scientific methods of review in formulating those opinions and again, as a threshold matter, the studies, publications and data upon which he relied are sufficiently reliable as to overcome Defendants' threshold challenge, *with the exception of Dr. Grossman's opinion that "pioglitazone may induce tumors of the bladder."* This Court has considered the five illustrative factors noted below and identified in Daubert and concluded that, with the exception of the opinion that pioglitazone may induce tumors of the bladder, they either weigh in favor of the admissibility of Dr. Grossman's opinions and foundational underpinnings or, alternatively, do not weigh in favor of the exclusion of the challenged opinions and foundational underpinnings.

#### **B. Rule 702/Daubert Factors**

After full review of all argument, evidence and supporting documentation, this Court finds the five factors identified in Daubert, either weigh in favor of admissibility of Dr.

---

<sup>28</sup> Id. at 24-47.

<sup>29</sup> Id. at 47-48.

<sup>30</sup> Id. at 48-50.



Grossman's causation opinions (except for his opinion that pioglitazone may induce tumors of the bladder) or do not weigh in favor of their exclusion of the challenged evidence.

- **Testability.** On its face, Dr. Grossman used methods of review that are well-established in those realms of science where carcinogenicity is determined, and these methods have been well-studied and tested. Similarly, the studies on which Dr. Grossman relies are founded on accepted scientific testing. As a threshold matter, the testability of the foundational underpinnings of Dr. Grossman's opinions support a finding of admissibility. The fact that Dr. Grossman has not engaged in independent testing of pioglitazone, but relies on published studies and case materials produced by the Defendants, is not fatal under the circumstances in this case because he has used an acceptable review methodology and the underlying foundational underpinnings have been tested.
- **Peer Review.** Dr. Grossman has cited a great many peer-reviewed publications that provide scientific support for his opinions. While it does not appear Dr. Grossman's specific opinions in this case have been subjected to peer review, this Court finds the *underlying studies* relied upon, incorporated, and used as foundational support for his conclusions, are and have been sufficiently subject to peer review and are accepted within the relevant scientific community. The absence of peer review for Dr. Grossman's opinions, in and of itself, does not invalidate Dr. Grossman's opinion when otherwise accepted review methodology has been employed to extrapolate information from peer-review publications. Dr. Grossman's heavy reliance on identified peer-reviewed publications, studies, and information – together with his discussion and consideration of those studies he finds unpersuasive – lend strong support for the argument in favor of admissibility of his opinion and foundational support for his conclusions, as a threshold matter.
- **Rate of Error.** Each underlying study relied upon by Dr. Grossman has a rate of error attached to the theory or technique used and is readily available for review and cross examination. The absence of a rate of error as to his specific opinions should not be fatal in the face of such error rates as to each underlying study.
- **Standards and Controls.** Dr. Grossman is a highly-qualified urologic oncologist who has conducted his investigation and developed his opinions, in this matter, in compliance with the standards and controls under which he normally operates in his professional life. This Court finds those standards and controls lend strong support for the argument of/for reliability of Dr. Grossman's opinions, as a threshold matter.
- **General Acceptance.** Dr. Grossman's report provides ample evidence his review methodology is generally-accepted in the scientific community and that his investigation is fully consistent with those generally-accepted principles even though it has not necessarily, itself, been replicated by another. Dr. Grossman's process employed, conclusions reached (after exception of his opinion that pioglitazone may induce tumors in the bladder), and opinions posted have been guided by scientifically-accepted processes found within the accepted scientific method, and stand upon a foundation of independent peer-reviewed studies and articles.

Consequently, this factor argues for allowing presentation of Dr. Grossman's opinions to the trier of fact, as a threshold matter.

This Court, also, notes, that unlike in Brown, in the instant matter, the opinions Dr. Grossman offers are not based merely on his "education and expertise." Dr. Grossman relies on multiple studies and publications; as well as extensive data; and utilizes the EPA Guidelines for Carcinogen Risk Assessment (which incorporate, to some extent the Bradford Hill criteria);<sup>31</sup> the World Health Organization's statement on the Evaluation of Carcinogenic Risks to Humans; and the National Toxicology Program's Process for creating its Report on Carcinogens in conducting his investigation and reaching his opinions. Had Dr. Grossman merely relied on his "education and expertise" as did the expert in Brown, Defendants' argument would be more persuasive, however, that is not the case. This Court finds that, with the exception of his opinion pioglitazone may induce tumor development in bladders, Dr. Grossman's opinions do not fail the threshold test of Brown, and that the Plaintiffs have met their *prima facie* burden of demonstrating, as a threshold matter, that Dr. Grossman's opinions are admissible.

### C. The Defendants' Challenges

The Defendants argue Dr. Grossman's conclusions are not reliable and, therefore, he should be precluded from testifying that Actos® causes bladder cancer in humans.<sup>32</sup> Defendants

---

<sup>31</sup> This Court has reviewed the Guidelines for Carcinogen Risk Assessment and finds the primary distinguishing factor of the EPA's approach is that the agency's investigators are required to look at all evidence available to them and to develop a narrative that addresses the weight of the evidence. Although the Bradford Hill factors are essential to evaluating the weight of epidemiological evidence, EPA investigators are not limited to epidemiological data in their efforts to determine carcinogen risks. The Defendants have not objected to Dr. Grossman's use of these more broadly-applicable guidelines. This Court agrees Dr. Grossman's choice is appropriate within the context of his opinion. Federal courts have approved the use of the Guidelines in a variety of settings and circumstances. *See, e.g., The American Bald Eagle v. Bhatti*, 9 F.3d 163 (1<sup>st</sup> Cir. 1993); Public Citizen v. Young, 831 F.2d 1108 (D.C. Cir. 1987); Natural Resources Defense Counsel, Inc. v. Environmental Protection Agency, 824 F.2d 1211 (D.C. Cir. 1987); In re: Methyl Tertiary Butyl Ether ("MTBE") Products Liability Litigation, 2008 U.S. Dist. LEXIS 50255 (S.D.N.Y. 2008); U.S. v. Phillip Morris USA, Inc., 449 F.Supp.2d 1 (D.C.D.C. 2006); Magistrini v. One Hour Martinizing Dry Cleaning, 180 F.Supp.2d 584 (D.N.J. 2002).

<sup>32</sup> Memorandum, at 1.

argue his “erratic and unreliable” use of the Bradford Hill criteria<sup>33</sup> justifies the exclusion of his opinions from the trial of this matter. The Defendants further argue that Dr. Grossman did not reliably apply generally accepted methodology; he violated his profession’s definition of proper scientific method by predicated his opinions on an inadequate factual basis and inconsistently applying epidemiological principles when analyzing and weighing the clinical data he reviewed; and, therefore, his opinions are factually unfounded and methodologically unsound.<sup>34</sup>

The structure of the Grossman Report includes, first, his investigation and how he reached his conclusions, a list of his opinions, followed by a description of his methodology, and a list of the evidence supporting his conclusions.<sup>35</sup> The Report later addresses “Pioglitazone and Expert Opinions on the Risk of Bladder Cancer”; in this section is a list of all of the literature he has reviewed, along with a description of his view of each study, the study’s role in his analysis, and his conclusions.<sup>36</sup> Regrettably, the Defendants’ arguments do not always reflect an appreciation of the separate roles and purposes of these two sections of the Report and tend to conflate and blend the two, to the disadvantage of Defendants’ argument. However, a careful review of the two sections establishes significant distinction as between the two.

The Defendants’ challenges, it would seem, fall into three categories: (a) a reiteration of the same types of objections asserted in various other Daubert motions and previously ruled upon by this Court in the Daubert motions preceding this motion (the “core” objections); (b) objection to the alleged advocacy on the part of Dr. Grossman; and (c) the challenge to Dr. Grossman’s

---

<sup>33</sup> Memorandum, at 3.

<sup>34</sup> Memorandum, at 1.

<sup>35</sup> Grossman Report.

<sup>36</sup> Grossman Report, at 24-47.

opinion concerning the potential for pioglitazone to induce tumors in the bladder. Each of these three categories will be addressed below.

### **1. Reiterated Arguments**

This Court has ruled within multiple Rulings on preceding Daubert motions [Rec. Docs. 3771 and 3779 in particular] on virtually all of the arguments presented by the Defendants in the instant motion as to general causation and Defendants' objections thereto. The instant motion does not persuade this Court to change its rulings as to the same arguments. Consequently, rather than reiterating those rulings at length herein, this Court adopts and incorporates rulings as to general causation found in Rec. Docs. 3771 and 3779 to address Defendants' "core arguments" as to general causation.

- ***The Plaintiffs' Theory of General Causation, specifically of presentation within One Year of Exposure***

Dr. Grossman's opinions and analysis support the Plaintiffs' theory of general causation as to cases of bladder cancer which present within one year of exposure to Actos. The gravamen of the dispute between the Plaintiffs and the Defendants as to Dr. Grossman's investigation, analysis, opinions, and conclusions – together with the role that those opinions and conclusions play in the Plaintiffs' overall theory of general causation – has been addressed to some degree in this Court's Memorandum Ruling: Development of Bladder Cancer Within One Year of Exposure [Rec. Doc. 3771] which is incorporated and adopted herein.

- ***Temporal Association***

In making their argument as to temporal association, the Defendants make no reference to the Grossman Report, nor in any way refer to *any specifics* of Dr. Grossman's opinions or how he does or does not support those opinions. Again, Defendants' put forth unsupported assertion and present generic arguments which this Court, regrettably, has seen before in the previous

Daubert motions. For example, Defendants suggest Dr. Grossman “ignored” the basic principle requiring a temporal association in arriving at his opinions,<sup>37</sup> and that he “ignored” other known risk factors for diabetes,<sup>38</sup> together with new arguments based upon characterizations that border on misrepresentation.<sup>39</sup> However, Defendants give no evidence, specific argument, or support for these bald assertions.

Because the temporal association challenge to Dr. Grossman’s report and opinions is similar to challenges asserted in response to the Plaintiffs’ general causation theory, Dr. Delacroix’s report and opinions, as well as Dr. Schneeweiss’ report and opinions, this Court adopts and incorporates those portions of the Memorandum Ruling: Dr. Scott Delacroix, Urologic Oncologist [Rec. Doc. 3779], and this Court’s Memorandum Ruling: Sebastian Schneeweiss, M.D., S.M., S.DC.D., F.A.C.E., F.C.P., F.I.S.P.E. [Rec. Doc. 3829], in addition to the Memorandum Ruling: Development of Bladder Cancer Within One Year of Exposure [Rec. Doc. 3771], to supplement the instant ruling and to address Defendants’ anemic argument as to this point.

---

<sup>37</sup> Memorandum, at 4. This Court notes, even a cursory reading reveals Dr. Grossman did not ignore the Defendants’ “temporal association” argument, nor did he limit himself to simply refusing to reject data related to bladder cancers occurring in the first year of clinical studies as Defendants’ argument implies. Instead, he openly declared that Takeda’s decision to eliminate such data from their analyses, in his opinion, “was not appropriate either methodologically or scientifically. The trials were controlled trials; in light of the evidence it was inappropriate to ignore the possibility of increased risk from short-term use. In addition, both of the letters issued by Takeda [to governmental agencies] clearly state that ‘a possible risk after short term treatment cannot be excluded.’” (Grossman Report, at 8-9.) Again, disagreement and explanation does *not* equate to an ignoring of and Defendants’ persistence to put forth such a false argument does not serve Defendants well.

<sup>38</sup> Memorandum, at 6. The Grossman Report contains four pages of discussion of risk factors other than Actos®.

<sup>39</sup> For instance, the Defendants state that Dr. Grossman “opines that Actos® not only can cause bladder cancer, but can do so in as short as one month.” (Memorandum, at 5, with a citation to the Grossman Deposition, at 269). This Court has reviewed both the Report and the Deposition, and finds that the cited testimony does not describe Dr. Grossman’s opinion, but his characterizing the PROactive results. Because Dr. Grossman has not actually issued any such opinion, this Court will not address any of the Defendants’ arguments associated with this “strawman” argument.

◦ *Consistency*

As before, the Defendants, again, argue alleged inadequacies in Dr. Grossman's opinions and supporting documentation without making any specific reference to his Report. This Court notes, again, however, that Dr. Grossman did not "ignore" allegedly inconsistent studies; rather, all but one of the studies argued by the Defendants were discussed in Dr. Grossman's Report. Dr. Grossman described the studies, identified their weaknesses, acknowledged when they did and did not reach statistical significance, and clearly explained how he perceives the studies, together with his use of them in his analysis.<sup>40</sup> Again, Defendants' assertion Dr. Grossman "ignored" those studies is, at best, unfortunate.

This Court would note the Defendants' inherent argument in their use of "consistent" as a synonym for "identical" is justified neither by the jurisprudence, nor by the scientific method; nor is it justified by common usage or by common sense. A study, whether or not it might or might not reach statistical significance, may be *consistent* with others if it finds a causal association, even when the strength of that association might vary and, thus, not be "identical." Consequently, Defendants' attempt to shift the legal inquiry from "consistency" to requiring studies "be identical" is, at very best, misplaced and wholly unpersuasive. To the extent Defendants' remaining challenge to Dr. Grossman on this point is similar to challenges asserted in response to Dr. Delacroix's report and opinions, and Dr. Schneeweiss' report and opinions,

---

<sup>40</sup> See Grossman Report, at 42-43 (discussion of Azoulay study, which demonstrates consistency of evidence and specificity of findings); 43 (discussion of Mantani study, which improperly omitted information demonstrating a consistently elevated risk of bladder cancer with exposure to pioglitazone, but still demonstrated an increased risk of bladder cancer with increasing length of exposure); 43-44 (discussion of Hsiao study, which showed significantly increased risk of bladder cancer with exposure to Pioglitazone and a dose-response relationship), 44 (discussion of Tseng study, which was a relatively small observational study that did not find a significantly increased risk of bladder cancer with Pioglitazone use). Dr. Grossman did not discuss the Chang study referenced by the Defendants; however, as the Defendants have not provided this Court with explanation about the Chang study, its strengths, weaknesses, or the use that Dr. Grossman ought to have made of it in his analysis, this Court cannot reasonably consider their argument nor pass judgment on whether the Chang study has any potential to impact the reliability of Dr. Grossman's opinions.



this Court adopts and incorporates those portions of the Memorandum Ruling: Dr. Scott Delacroix, Urologic Oncologist [Rec. Doc. 3779], and this Court's Memorandum Ruling: Sebastian Schneeweiss, M.D., S.M., S.DC.D., F.A.C.E., F.C.P., F.I.S.P.E. [Rec. Doc. 3829], to supplement the instant ruling.

- *Allegedly Weak Association*

Beyond question, it is true Dr. Grossman claims support from studies that reveal “modest” causal associations between pioglitazone and bladder cancer; however, such “modest” causal associations are, nonetheless, associations and Dr. Grossman does not rely upon these studies alone, nor does he rely on only epidemiological studies, but looks more broadly. Nonetheless, Dr. Grossman's Report demonstrates he notes those studies showing the lower relative risk, as well as those that did not reach statistical significance, and points out those studies were not the pillars upon which his opinions were founded, but were merely included as added weight to support the correctness of his conclusions. So long as there is statistically significant, reliable evidence supporting causation, the Fifth Circuit does not frown upon experts' use of additional evidence to further strengthen the conclusion, even if the additional evidence might not, in and of itself and standing alone, justify a conclusion as to causation.<sup>41</sup>

To the extent the Defendants' remaining challenge as to the causal association between pioglitazone and bladder cancer is similar to challenges asserted in response to the Plaintiffs' general causation theory, Dr. Delacroix's report and opinions, and Dr. Schneeweiss' report and opinions, this Court adopts and incorporates those portions of the Memorandum Ruling: Dr. Scott Delacroix, Urologic Oncologist [Rec. Doc. 3779], this Court's Memorandum Ruling:

---

<sup>41</sup> See, e.g., Wells v. SmithKline Beecham Corporation, 601 F.3d 375, 380 (5<sup>th</sup> Cir. 2010) (“this court has frowned on causation conclusions bereft of statistically significant epidemiological support”); Knight v. Kirby Inland Marine, Inc., 482 F.3d 347, 354 (5<sup>th</sup> Cir. 2007) (“where an expert otherwise reliably utilizes scientific methods to reach a conclusion, lack of textual support may ‘go to the weight, not the admissibility’ of the expert's testimony”).

Sebastian Schneeweiss, M.D., S.M., S.D.C.D., F.A.C.E., F.C.P., F.I.S.P.E. [Rec. Doc. 3829] and the Memorandum Ruling: Development of Bladder Cancer Within One Year of Exposure [Rec. Doc. 3771], to supplement the instant ruling.

- ***Biologic Plausibility***

The Grossman Report and the Grossman Deposition do not reveal Dr. Grossman has reached any firm conclusions about the biological mechanisms by which pioglitazone promotes or induces bladder cancer. Specifically, he refers to various elements of the Plaintiffs' general causation theory and his focus does not appear to be *on proving any one, or more, mechanism*. The role of identifying one or more specific mechanism(s) appears to have been assigned to other of the Plaintiffs' experts, and is clearly addressed within the Plaintiffs' general theory of causation.<sup>42</sup> The question at hand in this challenge of this expert, therefore, is whether the fact Dr. Grossman does not opine as to *specifically how* pioglitazone allegedly causes bladder cancer in humans, should preclude him from testifying *that* pioglitazone allegedly can cause bladder cancer in humans. Were it true the Plaintiffs had no evidence directed at establishing the possible modes and mechanisms of action by which pioglitazone allegedly works to cause bladder cancer upon which Dr. Grossman could and does rely, this Court would strongly question whether Dr. Grossman's opinions could or should carry the day on their own. However, that is not the case. The Plaintiffs have developed a theory of general causation upon which Dr. Grossman's opinions can rely and of which Dr. Grossman's opinion constitute only a discrete portion. It is not necessary Dr. Grossman, *himself*, work out *how* pioglitazone interacts and results in cancer. Rather, within the evidentiary landscape painted by Plaintiffs, Dr. Grossman is free to rely upon the other experts and accept that pioglitazone *can* interact in the

---

<sup>42</sup> See Memorandum Ruling: Development of Bladder Cancer Within One Year of Exposure [Rec. Doc. 3771].



way argued. Of course, Defendants are free to engage in vigorous cross-examination on this point and the jury is free to disregard Plaintiffs' evidence and experts on this point and, if so, likely Dr. Grossman's testimony as to this issue might fail. Again, however, this Court finds this is a question for the trier of fact and not the gatekeeper.

To the extent the remaining challenge to Dr. Grossman's report and opinions is similar to challenges asserted in response to the Plaintiffs' general causation theory, Dr. Delacroix's report and opinions, and Dr. Schneeweiss' report and opinions, this Court adopts and incorporates those portions of the Memorandum Ruling: Dr. Scott Delacroix, Urologic Oncologist [Rec. Doc. 3779], and this Court's Memorandum Ruling: Sebastian Schneeweiss, M.D., S.M., S.D.C.D., F.A.C.E., F.C.P., F.I.S.P.E. [Rec. Doc. 3829], in addition to the Memorandum Ruling: Development of Bladder Cancer Within One Year of Exposure [Rec. Doc. 3771] to supplement the instant ruling.

## **2. Dr. Grossman as Advocate**

The Defendants object to the degree to which Dr. Grossman is, in their opinion, willing to act as an enthusiastic advocate. Defendants repeatedly argue Dr. Grossman is such a strong advocate his opinions should be found to be wholly unreliable,<sup>43</sup> however, at no time are they as explicit as to their disapproval of Dr. Grossman as in their Reply Brief.

Thus, it is not Dr. Grossman's conclusion that Defendants challenge, but rather Dr. Grossman's willingness to misapply the facts and data in order to advocate on behalf of Plaintiffs.<sup>44</sup>

The Defendants clearly have taken umbrage at *the manner* in which Dr. Grossman presents his findings, and, perhaps, his enthusiasm in doing so, however, the first half of the

---

<sup>43</sup> See, e.g., Memorandum at 9 (Dr. Grossman "chose to rely on studies favorable to his opinion while minimizing or outright dismissing findings that do not support his opinion").

<sup>44</sup> Reply, at 1.

quoted sentence reveals **Defendants do not challenge his conclusions.** “[I]t is not Dr. Grossman’s conclusion that Defendants challenge. . . .”<sup>45</sup> If Defendants admit and accept that Dr. Grossman’s *conclusions* are unexceptionable, and not challenged, then it must follow that his alleged “willingness to misapply facts and data” clearly did not lead him so far into objectionable territory where his conclusions are unsupported. This Court must and will take Defendants at their word that they do not challenge Dr. Grossman’s conclusion. Defendants disagreement with his application or as Defendants argue, misapplication of the facts and data, “in order to advocate,” is perhaps strong fodder for cross-examination, but for cross-examination, nonetheless.

In service to its role as gatekeeper, this Court has conducted a thorough review of both the Grossman Report and the Grossman Deposition, and finds no indication Dr. Grossman violated the tenets of scientific methodology by way of his objected to “advocacy” by, for instance as argued, testifying on the basis of information “derived from his dreams or some other exercise in absurdist thinking.” To the contrary, this Court found no testimony evoking or justifying such description, nor did Defendants cite this Court to any portion of Dr. Grossman’s report which might justify such unfortunate use of empty hyperbole. Rather, the cursory review this Court made in search of the possible basis of Defendants’ unsupported assertion found the Grossman Report well-tethered to consensus reality and, more importantly, to the scientific view of reality. Again, on its face, to use such inflammatory hyperbole does not serve any party and, in particular, the Defendants well, within legal argument. The Grossman Report, the Grossman Deposition, and the argument presented by Plaintiffs to this Court on the instant motion, demonstrate Defendants have not carried their burden to show Dr. Grossman’s opinions unreliable, irrespective of the enthusiasm with which he might articulate them. And, again, this

---

<sup>45</sup> Id.

Court notes *even Defendants admit “it is not Dr. Grossman’s conclusion that Defendants challenge . . . .”* The Defendants can address Dr. Grossman’s alleged advocacy by way of vigorous cross-examination.

### 3. Pioglitazone as potential initiator

Finally, the Defendants challenge the admissibility of Dr. Grossman’s opinion pioglitazone “may induce tumors of the bladder.”<sup>46</sup> The only scientific support for this statement provided by Dr. Grossman, in either his Report or his Deposition, is found at Page 28 in the Grossman Report:

It should also be noted that Pioglitazone has been shown to be genotoxic in cultured human lymphocytes by analyses of chromosomal alterations and sister chromatid exchange. Both of these tests are sensitive indicators of genotoxicity. This may result in part from oxidative DNA damage since pioglitazone treatment resulted in release of 8-OH-dG (8-hydroxy-2'-deoxyguanosine), an oxidative DNA damage biomarker. In rats, pioglitazone treatment was shown to induce dose dependent DNA damage measured by comet assay in liver cells and peripheral blood lymphocytes.

The two studies cited in this paragraph demonstrate pioglitazone’s effects on *lymphocytes and liver cells*, but do not appear to have included any finding associated with *bladder cells or bladder tumors*. Nor does Dr. Grossman provide evidence of a scientific bridge between the two, nor does he address the analytical gap between liver and lymphocytes and bladder or bladder cells – two separate and distinct organs of the body – in any fashion. Moreover, Dr. Grossman did not, in his deposition, identify any additional support for this opinion.

The Defendants argue the evidence cited by Dr. Grossman, that involves side effects in organs other than the bladder, cannot support his opinion about tumors in the bladder and this Court agrees. The Plaintiffs’ Opposition Memorandum does not expand the evidence that might support Dr. Grossman’s opinion, nor otherwise attempt to demonstrate the scientific relevance of

---

<sup>46</sup> The Grossman Report, at 4, Opinion 6.

the two cited studies to *human bladders*. An expert's opinion and testimony must be reliable *at each and every step of the analysis or it is inadmissible*.<sup>47</sup> A court must especially mind the analytical gap that can exist between an expert's opinions and the studies on which he relies in forming those opinions.<sup>48</sup> While Dr. Grossman adequately supports the majority of his opinions with citations to relevant, peer-reviewed articles, Dr. Grossman did not do so as to this portion of his opinion and this Court finds the analytical gap between the two studies cited by Dr. Grossman and his opinion that pioglitazone induces tumors in the bladder is unaddressed and too great to pass review by the gatekeeper and, therefore, this Court finds this portion of his opinion is not sufficiently reliable to be admissible pursuant to Rule 702 of the Federal Rules of Evidence.

Dr. Grossman will not be permitted to present to the jury his opinion that pioglitazone may induce tumors in the bladder [in humans].

### III. EVIDENTIARY HEARING

The Defendants requested this Court agree to hear live testimony from the experts prior to ruling on the instant motion; this Court carefully considered the Defendants' request. The decision of how to go about ruling on the instant motion is squarely within this Court's discretion.

The trial court must have the same kind of latitude in deciding *how* to test an expert's reliability, and to decide whether and when special briefing or other proceedings are needed to investigate reliability, as it enjoys when it decides whether or not that expert's relevant testimony is reliable. Our opinion in Joiner makes clear that a court of appeals is to apply an abuse-of-discretion standard when it reviews a trial court's decision to admit or exclude expert testimony. That standard applies as much to the trial

---

<sup>47</sup> Knight, 482 F.3d at 355 ("The reliability analysis applies to all aspects of an expert's testimony; the methodology, the facts underlying the expert's opinions, the link between the facts and the conclusion").

<sup>48</sup> See, e.g., General Electric v. Joiner, 522 U.S. 136, 146-47, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997), as cited in Knight, 482 F.3d at 355.

court's decisions about how to determine reliability as to its ultimate conclusion. Otherwise, the trial judge would lack the discretionary authority needed both to avoid unnecessary "reliability" proceedings in ordinary cases where the liability of an expert's methods is properly taken for granted, and to require appropriate proceedings in the less usual or more complex cases where cause for questioning the expert's reliability arises. Indeed, the Rules seek to avoid unjustifiable expense and delay as part of their search for truth and the just determination of proceedings.<sup>49</sup>

This Court reviewed the extensive briefing provided by both parties, as well as the large number of exhibits, including expert reports, depositions, and other documents, and concluded the nature of the challenges presented and the arguments made did not illustrate a need for live testimony. Live testimony would not be likely to contribute to any greater understanding of the nature of the dispute than can be and has been found in a careful reading and analysis of the briefs and accompanying evidence and documentation. The request for an opportunity to present live testimony in an evidentiary hearing is DENIED.

### CONCLUSION

For the foregoing reasons, the Defendants' Motion to Exclude Testimony of Plaintiffs' Expert, Herbert Barton Grossman, M.D., shall be DENIED IN PART and GRANTED IN PART.

THUS DONE AND SIGNED this 8 day of January, 2014.



REBECCA F. DOHERTY  
UNITED STATES DISTRICT JUDGE

---

<sup>49</sup> Kumho Tire, 526 U.S. at 152-53 (emphasis in original) (citations and quotations omitted).